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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/508,083	07/03/2000	WOLF GEORG FORSSMANN	P65123US0	8457

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EXAMINER	
SCHNIZER, HOLLY G	

ART UNIT	PAPER NUMBER
1653	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No. 09/508,083	Applicant(s) FORSSMANN ET AL.	
	Examiner Holly Schnizer	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *60-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *60-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

Claims 38-59 were cancelled and Claims 60-77 were added in the Amendment filed February 13, 2003 (Paper No. 14). Therefore, Claims 60-77 are pending and will be considered in this Office Action.

Objections Withdrawn

The objection to the Specification and Claims because they failed to comply with the sequence rules is withdrawn in light of the amendments.

Rejections Withdrawn

The rejection of Claims 41-55 and 57-59 rejected under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in light of the cancellation of these claims.

The rejection of Claims 41-55 under 35 U.S.C. 102(b) as being anticipated by Buckley et al. (WO 91/11457, 1991; ref. AD in IDS of Paper No. 7) is withdrawn in light of the cancellation of the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 64-77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition containing a compound according to claim 60 for the therapy of insulin-independent diabetes mellitus and a method of using the composition in a method of treating insulin-independent diabetes mellitus, does not reasonably provide enablement for pharmaceutical compositions containing the compound according to claim 60 for the therapy of insulin-dependent diabetes mellitus, MODY, secondary hyperglycaemias in connection with pancreatic diseases (chronic pancreatitis, pancreatectomy, haemochromatosis), endocrine diseases (acromegaly, Cushing's syndrome, phaeochromocytoma, or hyperthyreosis, hyperglycaemias induced by drugs (benzathiadiazine salidiuretics, diazoxide, or glucocorticoids), pathologic glucose tolerance, hyperglycaemias, dyslipoproteinaemias, obesity, hyperlipoproteinaemias, and/or hypotonias or methods of treating these diseases using the composition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

It would require undue experimentation for one of skill in the art to practice the claimed invention commensurate in scope with the claims. Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d, 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include (1) quantity of experimentation, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state

of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

A response to Applicants arguments follows the rejection below.

Statement of Rejection

The nature of the invention involves the discovery that GLP-1 (7-34)(peptide of Claim 38) has a longer half-life than that of GLP-1 (7-36) amide and that infusion of GLP-1 (7-34)COOH and GLP-1(7-34)Amide in equimolar amounts results in higher insulin release and higher reduction of glucose levels than GLP-1(7-36) Amide does (see p. 2-3 of present Specification).

The Claims broadly encompass the intended use of claimed peptides having the sequence of GLP-1(7-34) and modified peptides having that sequence in the treatment of a wide variety of diseases of various tissues, wherein each disease involves unique mechanism and unique set of involved factors and problems.

The state of the prior art and the relative skill in the prior art is such that the peptide of present Claim 60 is well known in the prior art and has been suggested for use in the treatment of insulin-independent diabetes mellitus (non-insulin dependent or type II diabetes) (see prior art references below). However, there appears to be no teaching or suggestion of using peptides similar or identical to that of Claim 60 in the treatment of the additional diseases listed in present Claim 64-65. While the level of relative skill in the art is high, one of skill in the art would require some guidance as to how the peptide is related to each disease state, how much of the peptide to administer, and what mode of administration to obtain any expectation of success in treatment.

Drucker (Endocrinol. (2001) 142(2): 521-527) indicates that even for the treatment of diabetes, further evaluation/experimentation of the efficacy of GLP-1 in treating diabetes is necessary including further research on how the protein can be administered (see p. 525, Col. 1, last paragraph).

The only guidance provided in the Specification is a mere mention that the peptides of the invention could be used in the treatment of the various diseases (p. 10). The Specification also suggests a wide range of dosages but does not specify what diseases or conditions those dosages could be used to successfully treat (p. 13).

There are no working examples in the present Specification.

In light of the factors described above (no teaching or understanding of how GLP-1 is related to the wide variety of disease claimed; recognition in the art that, even in the case of treating diabetes, further research is necessary to determine what modes and dosages of GLP-1 could possibly be effective in treatment; lack of any teaching, in the Specification or prior art, of forms of administration or dosages for any specific disease) it appears that it would be highly unpredictable whether or not the GLP-1 proteins claimed would be effective to treat the wide variety of diseases claimed. Moreover, what administration mode and dosage would allow successful treatment of any given disease would also be highly unpredictable.

Therefore, undue experimentation would be required to characterize the involvement of the claimed GLP-1 proteins in each specific disease and determine what form of administration and what dosage would be effective to treat each specific disease. To practice the instant invention in a manner consistent with the breadth of the

claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the determination of the role (if any) played by the GLP-1 protein in each disease state and then the determination of how the protein can be effectively administered to treat each disease. It is this additional characterization of the protein, its relationship to disease, and effective administration forms that is required in order to make and use the claimed proteins for their intended use that constitutes undue experimentation.

Response to Applicant's argument:

Screening a protein to determine if and how it can be used to treat various diseases is not routine in the art.

Applicants contend that enablement is shown because screening a protein for biological activity is routine and Applicants point to Ex parte Mark 12 USPQ2d 1904 (BPAI 1989) to support their contention. This argument has been considered but is not deemed persuasive because to practice the invention would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the determination of the role (if any) played by the GLP-1 protein in each disease state and then the determination of how the protein can be effectively administered to treat each disease. It is this additional characterization of the protein, its relationship to disease, and effective administration forms that is required in order to make and use the claimed proteins for their intended use that constitutes undue experimentation. The present

case is different from that presented in Ex parte Mark (12 USPQ2d 1904 (BPAI 1989) because it is more complex. To practice the full scope of the claimed invention in the case at issue in Ex parte Mark required merely making a mutant protein and screening for an activity. In other words, determining which proteins could be used merely required answering a yes or no question that could be determined through routine screening of proteins. In contrast, the present case requires determining whether the GLP-1 protein could be used to treat each disease of the claim in the absence of any guidance as to how the protein might be involved in the disease, then determining the amount to administer, the mode of administration, and timing of administration. Thus, to practice the present invention does not require merely answering a yes or no question (does the protein have activity or not) using repetitive and routine screening techniques as was the case in Ex parte Mark, but requires the understanding of how the protein is involved in each disease state and, if determined useful in treating a particular disease, a determination of how to deliver therapeutically significant amounts of the protein to the appropriate target to successfully treat the disease. As stated in the previous Office Action (last 4 lines of p. 7 of Paper No. 13), Drucker (Endocrinol. (2001) 142(2): 521-527) indicates that even for the treatment of diabetes, further evaluation/experimentation of the efficacy of GLP-1 in treating diabetes is necessary including further research on how the protein can be administered (see p. 525, Col. 1, last paragraph). Drucker states, "development of safe, well-tolerated GLP-1 formulations that exhibit prolonged bioactivity in vivo remain major challenges for implementation of successful GLP-1 therapeutics programs" (p. 525, Col. 1, section

titled "GLP-1 and GLP-2: Future Research Directions"). Therefore, without guidance as to how to use the protein of the invention to treat any of the diseases listed in the claims and in light of the evidence provided in Drucker which shows the challenges that are present in determining whether a protein can be used in a method of treatment, one of skill in the art would not have a reasonable expectation of success in using the claimed protein in a method of treating any of the many diseases listed in the claims. Therefore, the rejection is maintained for the reasons cited in the previous Office Action.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 60-62, 64, and 66-77 are rejected under 35 U.S.C. 102(b) as being anticipated by Danley et al. (EP 0 619 322, 1994).

A response to Applicants arguments follows the statement of rejection below.

Rejection:

Danley et al. meets the limitations of the claims because Danley et al. disclose a compound having identical general formula to that of the compound of present Claim 60 (SEQ ID NO:1) (see sequence alignment attached to the previous Office Action of

Paper No. 13, SEQ ID NO: 5 of Danley et al., and p. 47, clms. 1 and 2, SEQ ID NOs: 5 and 7 of Danley et al.). Danley et al. discloses making carboxyamide derivatives of the disclosed peptides for peptide synthesis and thus meets the limitations of Claims 61-62 (see p. 17, lines 28-30). Danley et al. is considered to meet the limitations of Claims 68-77 because the pharmaceutical compositions of Danley et al. contain the same compound and are therefore patentably indistinguishable from that of the present Claims 68-77. Danley et al. meets the limitations of Claims 64-67 because Danley et al. teaches that the compositions containing the compounds are used in treatments of insulin-independent diabetes and are in a form by which release is attained in a long-lasting or pulsatile manner and wherein the form is suitable for subcutaneous, intravenous, peroral, intramuscular, or transpulmonary administration (see p. 60, clm. 14; p. 17, line 56; and p. 18, lines 4-5).

Response to Applicants arguments:

Applicants argument that Danley et al. does not specifically describe GLP-1 (7-34) amide or suggest that the amide is the preferable modification for gaining more insulinotropic effect is not persuasive because Danley et al. describe and claim a peptide identical to that of Claim 60 (see SEQ ID NO:5 of Danley et al.) and a method of using the peptide in treatment of non-insulin dependent diabetes (see claim 1 of Danley et al. for example). Thus, the rejection is maintained for the reasons cited in the previous Office Action and repeated below.

Claim 60-62, 64, and 66-77 is rejected under 35 U.S.C. 102(b) as being anticipated by Habener (US Patent No. 5,118,666, 1992).

A response to Applicants arguments is provided following the rejection below.

Rejection

Habener meets the limitations of Claim 60-62 because Habener discloses a compound having identical general formula to that of the compound of Claim 60 (see sequence alignment attached to the Office Action of Paper No. 13 and clm.1A of Habener) and a pharmaceutically acceptable amide derivative of the compound wherein an alkyl group is used as an amino protecting group (see Col. 6, lines 20-26).

Habener meets the limitations of claim 64 because Habener teaches a method of treating mature onset diabetes using a composition comprising the disclosed compound. Habener meets the limitations of Claims 66-67 because Habener teaches that the compositions can be administered intravenously, intramuscularly, or subcutaneously (Col. 7, lines 64-66) in a long-lasting manner (see Col. 8-9).

Habener meets the limitations of Claims 68-77 since Habener teaches a composition containing a compound identical to that of present Claim 60 (which is the compound contained in the composition of present claims 68-77). The Habener composition and the composition of the present invention appear to be patentably indistinguishable since both contain the same components.

Response to Applicants arguments

Applicants argument that Habener is silent with respect to GLP-1 (7-34) is not persuasive because Habener discloses and claims a compound having a sequence

identical to that of SEQ ID NO:1 of the present invention (see sequence alignment attached to Paper No. 13 and claim 1(A)(a) of Habener). Habener also indicates that the peptide of claim 1 has greater insulinotropic activity than that of GLP-1 (1-36 or GLP-1 (1-37 (see Col. 18, lines 40-66, especially lines 63-66). Thus, the rejection is maintained for the reasons cited in the previous Office Action.

Thus, Claims 60-62, 64, and 66-77 appear to be anticipated by Habener and the rejection is maintained.

New Rejections necessitated by amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 62, and 66-67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 62 is indefinite for the limitation wherein R is –butyl-n. The term "R" refers to N-terminal modification of the compound of Claim 60. However, the specific modification, "-butyl-n" appears to refer to a C-terminal modification because of the dash before "butyl-n" and absence of a dash after "butyl-n". Therefore, the claim is unclear as to where the modification is to be made. A review of cancelled claim 40 appears to suggest that "n-butyl-" was intended. Correction is required.

Claims 66-67 are rejected to because the claims are drawn to methods but the limitations added in these dependent claims appear to refer to a product. For example, in Claim 66, when is a method "in a release form"? This rejection could be overcome by amending the claims to read consistently. An example of an appropriate amendment follows: for claim 66, substitute "in a release form by which the release is attained" with "wherein the composition is administered" and in claim 67, substitute "suitable for subcutaneous, intravenous, peroral, intramuscular, or transpulmonary administration" with "wherein the composition is administered subcutaneously, intravenously, perorally, intramuscularly, or transpulmonarily". Correction is required.

Conclusions

No Claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached on Monday through Wednesday from 8am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

Holly Schnizer
May 12, 2003

CHRISTOPHER S. F. LOW
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